REVIEW

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Role of Spinal Neurotransmitter Receptors in Itch: New Insights into Therapies and Drug Development

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SUMMARY

Targets for antipruritic therapies are now expanding from the skin to the central nervous system. Recent studies demonstrate that various neuronal receptors in the spinal cord are involved in pruritus. The spinal opioid receptor is one of the best-known examples. Spinal administration of morphine is frequently accompanied by segmental pruritus. In addition to μ-opioid receptor antagonists, κ-opioid receptor agonists have recently come into usage as novel antipruritic drugs, and are expected to suppress certain subtypes of itch such as hemodialysis- and cholestasis-associated itch that are difficult to treat with antihistamines. The gastrin-releasing peptide receptor in the superficial dorsal horn of the spinal cord has also received recent attention as a novel pathway of itch-selective neural transmission. The NMDA glutamate receptor appears to be another potential target for the treatment of itch, especially in terms of central sensitization. The development of NMDA receptor antagonists with less undesirable side effects on the central nervous system might be beneficial for antipruritic therapies. Drugs suppressing presynaptic glutamate-release such as gabapentin and pregabalin also reportedly inhibit certain subtypes of itch such as brachioradial pruritus. Spinal receptors of other neuromediators such as bradykinin, substance P, serotonin, and histamine may also be potential targets for antipruritic therapies, given that most of these molecules interfere not only with pain, but also with itch transmission or regulation. Thus, the identification of itch-specific receptors and understanding itch-related circuits in the spinal cord may be innovative strategies for the development of novel antipruritic drugs.

Introduction

Itch is a frequent symptom that accompanies various systemic as well as skin diseases. In the last two decades, research on the mechanisms of itch has intensified and a great progress has been achieved, though we are still far from complete clarification [1,2]. Antipruritic drugs are no longer restricted to peripherally acting agents such as antihistamines, which are ineffective for most pruritic diseases. Instead, targets for antipruritic drugs are expanding to include centrally located receptors such as opioid receptors. Currently, neurotransmitter receptors in the spinal cord are the most attractive targets for antipruritic treatments, as was shown in recent studies of gastrin-releasing peptide (GRP) receptors and the development of κ-opioid receptor (KOR) agonists. The purpose of this review is to describe the many spinal neurotransmitter receptors that are involved, or are expected to be involved, in itch, and to review them in terms of their potential as targets for antipruritic therapies.

Opioid Receptors

Endogenous opioid peptides, such as endorphins, enkephalins, dynorphins, and endomorphins, work as neuromediators as well as hormones and immunomodulators. They exert their effects through activation of three classes of receptors: μ, κ, and δ. Although opioid receptors are located in both peripheral and central nervous system, their involvement in pain/itch pathway has been investigated mainly in the central nervous system, often in relation to morphine. Morphine is one of the best-known μ-opioid receptor (MOR) agonists and has been used as analgesic agent for many centuries. As a cumbersome adverse event, epidural or spinal administration of morphine frequently causes segmental pruritus, whereas generalized itch, although rare, accompanies systemic administration of morphine [3,4]. Accordingly, intracutaneous administration of morphine induces mast-cell degranulation, and plasma levels of histamine are elevated after morphine is given intravenously [5]. This effect, however, is not

attenuated by naloxone, a MOR antagonist, suggesting that mechanisms independent of the MOR are involved in morphine-mediated histamine-release [6]. In contrast, itch after spinal administration of morphine is most probably histamine-independent, since spinally administered fentanyl, another full MOR agonist, induces itch without any histamine-release [5]. Moreover, antihistamines are relatively ineffective to treat pruritus caused by spinally applied morphine as compared to by systemically applied morphine [7]. The incidence and severity of itch after spinal application of morphine is dose-dependent [8]. The body distribution of morphine-induced itch is usually limited to the face, neck, and upper thorax [3]. Morphine-induced itch often spreads rostrally from the injection site [9], and can be inhibited by MOR antagonists [10], suggesting that MOR at the spinal cord level plays a critical role in morphine-induced itch. This is also supported by a monkey study showing that a peptidic MOR agonist evoked intense scratching when applied intrathecally, but not when applied intravenously [11]. Another monkey study has suggested that MOR in the medullary dorsal horn plays an important role in morphine-induced pruritus [12].

On the other hand, MOR antagonists such as naloxone and naltrexone have antipruritic potencies that are not restricted to morphine-induced itch. According to a double-blind placebo-controlled study in healthy human volunteers, histamine-induced itch can be significantly suppressed by naltrexone without affecting histamine-induced wheal/flare reactions or alloknesis [13]. This suggests a central antipruritic effect of naltrexone on histamine-induced itch. Naloxone and naltrexone also have effects on dialysis- and cholestasis-related itch, which are normally resistant to antihistamine therapies and difficult to control in most cases [14–16]. Of note, when MOR antagonists were applied in some patients with cholestatic pruritus, they simultaneously reduced itch and induced pain, indicating the involvement of MOR in controlling the balance between itch and pain in those patients [17].

When morphine is applied to decrease pain, it would not be beneficial if MOR antagonists would simultaneously be used to inhibit morphine-induced itch, since the same MOR is involved in both analgesia and itch [18]. In the meantime, recent studies have demonstrated that KOR agonists can attenuate MOR agonist-induced pruritus. They inhibit itch that occurs after intrathecal application of morphine without affecting analgesia [19]. Butorphanol, which is a partial MOR and KOR agonist and is used as analgesic [20], also reduces morphine-induced itch without reducing antinociceptive effects of morphine [21]. These indicate that KOR agonists are promising antipruritic agents for morphine-induced itch, and that KOR agonists exert their antipruritic effects most probably at the spinal level just like MOR agonists exert their pruritic effects there. Although KOR agonists also have binding affinities for MOR *in vitro* and might potentially play a role as MOR antagonists at high doses [22–24], antipruritic doses of KOR agonists did not antagonize morphine-induced analgesia or respiratory suppression, and their antipruritic effect was completely blocked by KOR antagonists *in vivo* in monkeys [19]. In addition, antipruritic effects of KOR agonists are independent of two KOR subtypes (KOR-1 and non-KOR-1) [19]. These indicate that the antipruritic effect of KOR agonists is mediated by KORs, independently of KOR subtypes, and is not due to their MOR antagonizing effects. Moreover, pre-clinical data show that KOR agonists do not only suppress morphine-induced itch but also suppress other types of itch including both histamine-dependent and -independent itch [25]. On the other hand, KOR antagonists do not have antipruritic potencies. They rather work as pruritogens in mice [26], although this is not the case in primates [27]. C-fos expression in the spinal cord of mice was induced by subcutaneous application of KOR antagonists or compound 48/80, which both provoked scratching behavior, and was inhibited by pretreatment with KOR agonists [28]. Thus, selective KOR agonists such as nalfurafine have gained much attention as novel antipruritic drugs for diverse types of pruritus. Indeed, clinical studies have successfully demonstrated the effects of nalfurafine on severe itch in hemodialysis patients [29,30]. These results also raise expectations for the treatment of other subtypes of intractable itch such as cholestasis- and tumor-associated itch.

Gastrin-Releasing Peptide Receptor

The GRP, which is a bombesin-like peptide, and its receptor, bombesin receptor-2 (BB_2), are broadly expressed in the central nervous system and gastrointestinal tract. GRP exerts various physiological functions such as hormone secretion, blood flow regulation, and smooth muscle contraction through activation of BB_2 [31,32]. The question of whether GRP and BB_2 are important mediators for itch/pain sensation, which had already been addressed in a study of BB_2 mutant mice [33], was investigated in detail by recent studies providing the following information [34,35]: In dorsal root ganglion (DRG) neurons, GRP is specifically expressed by a small subset of small- to medium-sized neurons that show co-localization with calcitonin gene-related peptide (CGRP) and with peripherin, a marker for unmyelinated neurons. This indicates that GRP is mainly, if not exclusively, generated by peptidergic unmyelinated C-fibers. In the dorsal horn of the spinal cord, GRP is distinctly localized in lamina I and the outer layer of lamina II (IIo). However, the mRNA of GRP is not detectable in the spinal cord, and most of GRP-positive fibers diminish after dorsal rhizotomy, indicating the pre-synaptic release of GRP from central endings of primary afferent neurons. In contrast, the mRNA of BB_2 is detectable by *in situ* hybridization in a distinct subset of neurons located in the marginal zone of dorsal horn, most probably restricted to lamina I [34]. BB_2-mutant mice had normal pain perception for mechanical and thermal stimuli, but demonstrated less scratching behavior when compound 48/80, chloroquine, or protease-activated receptor-2 (PAR_2) agonists were applied. Intrathecal administration of BB_2 antagonists reduced scratching behavior induced by those pruritogens in wild-type mice [34]. Those mice in which lamina I neurons expressing BB_2 were ablated by intrathecal application of bombesin-saporin showed deficit of scratching behavior to histamine, compound 48/80, serotonin, endothelin-1, chloroquine, and PAR_2 agonists. This deficit of scratching was not observed in BB_2-mutant mice in which bombesin-saporin could not bind to BB_2 but BB_2-expressing neurons were intact [35].

Another recent study has verified coexpression of GRP with the Mas-related G protein-coupled receptor (Mrgpr) member A3 (MrgprA3) in DRG neurons [36]. Mrgprs, consisting of more than 50 members, are exclusively expressed in peripheral sensory

neurons [37,38]. A study in mice showed that targeted disruption of the Mrgpr gene cluster reduces itch responses to chloroquine, but not to histamine, and also that MrgprA3, among the Mrgpr family, is the crucial receptor for chloroquine-induced itch [36]. Thus, the following hypothesis for chloroquine-induced itch can be suggested: chloroquine activates MrgprA3 on primary afferent nerve fibers in the skin. Subsequently, GRP is released from central endings of primary afferent nerves, which leads to activation of BB_2 in post-synaptic neurons of the spinal cord. This very attractive hypothesis remains to be proven by experiments verifying that activation of MrgprA3 directly leads to GRP release in the spinal cord.

The final conclusion about the role of GRP and BB_2 in itch, especially in humans, is still difficult to draw. Reduced scratching behavior to compound 48/80, cloroquine, and PAR_2 agonists in BB_2-mutant mice and antipruritic effects of BB_2 antagonists on those pruritogens, as mentioned above, can suggest the involvement of GRP and BB_2 in itch induction. However, it must also be mentioned that no significant difference was observed between BB_2-mutant and wild-type mice in their scratching behavior induced by histamine, endothelin-1, and serotonin [35], indicating that GRP/BB2 cannot solely explain the spinal itch pathway. Taken together, BB_2-expressing neurons, rather than GRP and BB_2, might play a more important role in itch conduction at the spinal cord level. Although the precise role of GRP/BB_2 in itch needs to be further explored, BB_2 seems to be a marker for itch-conducting neurons [39].

Glutamate Receptors

Glutamate is one of the major excitatory neurotransmitters in the spinal cord and exerts its effects when it binds to glutamate receptors such as *N*-methyl-$_D$-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and five kainate receptors. NMDA receptors are known to play a crucial role in two types of synaptic plasticity, long-term potentiation (LTP) and long-term depression (LTD), due to its voltage-dependent activation and high capacity for Ca^{2+} permeability [40]. NMDA receptors consist of many subunits, which are categorized into three subtypes (NR1, NR2, and NR3) and expressed in a broad area of the peripheral and central nervous system. The synaptic plasticity, which is known to be the fundamental mechanism for learning and memory processes, also contributes to central sensitization, when occurring in the pain pathway [41]. Namely, continuous noxious inputs from the periphery, for example, after injury or inflammation, lead to depolarization in the post-synaptic cells of the spinal cord, which subsequently remove the Mg^{2+} blockade from the NMDA receptors. Subsequent activation of NMDA receptors leads to Ca^{2+} influx and intracellular signal transduction cascades, resulting in the phosphorylation of ion channels in NMDA and other receptors. Thus, NMDA receptors are involved in the prolonged increase of spinal neuron excitability, i.e., central sensitization [42].

As a result of central sensitization, patients with chronic pain such as post-herpetic neuralgia feel pain even when only weak mechanical stimuli are given to the skin. They also feel enormous pain by light pin-pricking stimuli to the skin. Similar phenomena are observed in patients with chronic pruritus such as atopic dermatitis. Patients with atopic dermatitis feel itchy when weak mechanical stimuli that are normally non-pruritic are applied. Experimental studies with these patients have shown that intracutaneously applied histamine induces extraordinarily intensive itch [43]. Moreover, stimuli that are normally painful and suppress pruritus can induce itch in lesional skin of patients with atopic dermatitis [44]. These phenomena indicate a significant role of central sensitization in chronic pruritus as well.

It is reasonable that NMDA receptor antagonists such as ketamine have been used in many preclinical and clinical trials in the hope of their analgesic effects [45–47], since NMDA receptors apparently play a crucial role in central sensitization within the pain pathway. These trials have actually demonstrated positive analgesic effects of NMDA receptor antagonists. Considering the similarity of central sensitization in pain and itch pathways, NMDA receptor antagonists might also be effective for the inhibition of itch, as has already been demonstrated [48,49].

The biggest problem hampering the use of NMDA receptor antagonists to treat pain and itch is their unacceptable adverse effects such as sedation, motor coordination disorder, memory disorder, and psychedelic effects. In this regard, NR2B subunit receptor antagonists may be the most promising among NMDA receptor blockers. They might have analgesic effects with a lower possibility of adverse events, since NR2B receptors are exclusively located in the superficial layers of the spinal cord dorsal horn that are associated with pain and itch pathways. It is a great advantage that NR2B are only marginally expressed in the cerebellum [50,51]. Indeed, NR2B receptor antagonists such as ifenprodil are effective in treatment of pain and have less adverse effects as compared to nonselective NMDA receptor antagonists, although analgesic effects of NR2B receptor antagonists might predominantly be mediated at the supra-spinal level rather than the spinal level [52]. Further investigation of NR2B selective antagonists with less severe side effects on the central nervous system is demanded in order to determine their potential as antipruritic agents.

In terms of glutamate release inhibition, analgesic effects of gabapentin and pregabalin are also important to note. Both drugs were originally developed as antiepileptic drugs, and are currently used widely for analgesic purposes, especially to treat neuropathic pain [53]. Their analgesic effects may derive from binding to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, especially at the spinal cord level, which inhibits pre-synaptic Ca^{2+} influx and leads to decreased glutamate release and synaptic transmission [54,55]. This indicates that gabapentin and pregabalin might also be effective for some subtypes of itch, especially neuropathic itch such as post-herpetic and brachioradial pruritus. Indeed, some clinical studies have already reported antipruritic effects of gabapentin and pregabalin [56–59].

Neurokinin-1 Receptor

Substance P (SP) is a neuropeptide that belongs to the tachykinin family. Among the three known tachykinin receptors, i.e., neurokinin-1, -2, and -3 receptors, neurokinin-1 receptor (NK_1R) has the highest affinity for SP and is broadly expressed in the peripheral and central nervous system [60]. Considerable evidence indicates the involvement of SP and NK_1R in peripheral and central pain transmission. On the other hand, intradermally applied

SP induces scratching behavior in mice, indicating a role of SP in pruritus as well [61]. Neither histamine nor any other mast cell mediator seems to be involved in SP-induced itch in mice, since SP-induced scratching is not blocked by antihistamines [25], and is also observed in mast cell-deficient mice [61]. In contrast, a recent study in African naked mole-rats has shown that SP in spinal post-synaptic nerves is necessary for histamine-induced scratching behavior [62]. Leukotriene B_4 may mediate SP-induced peripheral itch in mice [63]. Whether SP plays an important role in itch induction in human skin is still controversial. Increased local levels of SP and NK_1R associated with pruritic skin diseases such as atopic dermatitis [64], urticaria [65], and psoriasis [66] support the idea that SP is involved in itch induction in humans, although SP-induced itch in humans seems to be at least partly mediated via histamine release from mast cells [67]. However, intradermal application of SP in an amount sufficient to induce vasodilatation and protein extravasation does not induce any itch sensation in human subjects [68], indicating that physiological levels of SP hardly play a role as an acute itch mediator in human skin.

Conversely, a recently published study suggests the involvement of NK_1R in itch at the central level [69]. According to this report, spider venom, which is pruritogenic in wild-type mice, did not induce any scratching behavior in NK_1R-deficient mice. Moreover, spider venom-induced scratching was blocked only by systemically applied, but not locally applied, NK_1R antagonists. This suggests the central involvement of NK_1R in itch, probably at the spinal cord level. The hypothesis that the NK_1R expressed in the spinal cord plays an important role in itch/pain transmission is supported by studies in rodents demonstrating a high expression of NK_1R in the superficial dorsal horn of the spinal cord including the lamina I [70–75]. Central endings of primary afferent nerves release SP when they are incubated with PAR_2 agonists [76], indicating that protease-release under inflammatory conditions in the spinal cord (e.g., after spinal cord injury) may regulate inflammation and pain via SP release and NK_1R activation. Hyperalgesia caused by subcutaneous injection of PAR_2 agonists is diminished in NK_1R-deficient mice and in rats pretreated with NK_1R antagonists [77]. Moreover, ablation of NK_1R-expressing dorsal horn neurons reduces hyperalgesia in pain models [78,79]. These data strongly suggest that SP and NK_1R are involved in pain transmission at the spinal cord level. However, previous studies have rather demonstrated only a poor antinociceptive effect of NK_1R antagonists [80–82]. A possible antipruritic effect of aprepitant, a NK_1R antagonist that also has affinities for NK_2R and NK_3R to some extent, has been reported in relation to the treatment of the Sézary syndrome [83]. A very recent study has shown that aprepitant is effective in patients with various types of chronic pruritus [84]. A therapeutic value of NK_1R antagonists for itch inhibition remains to be confirmed by large-scale clinical studies.

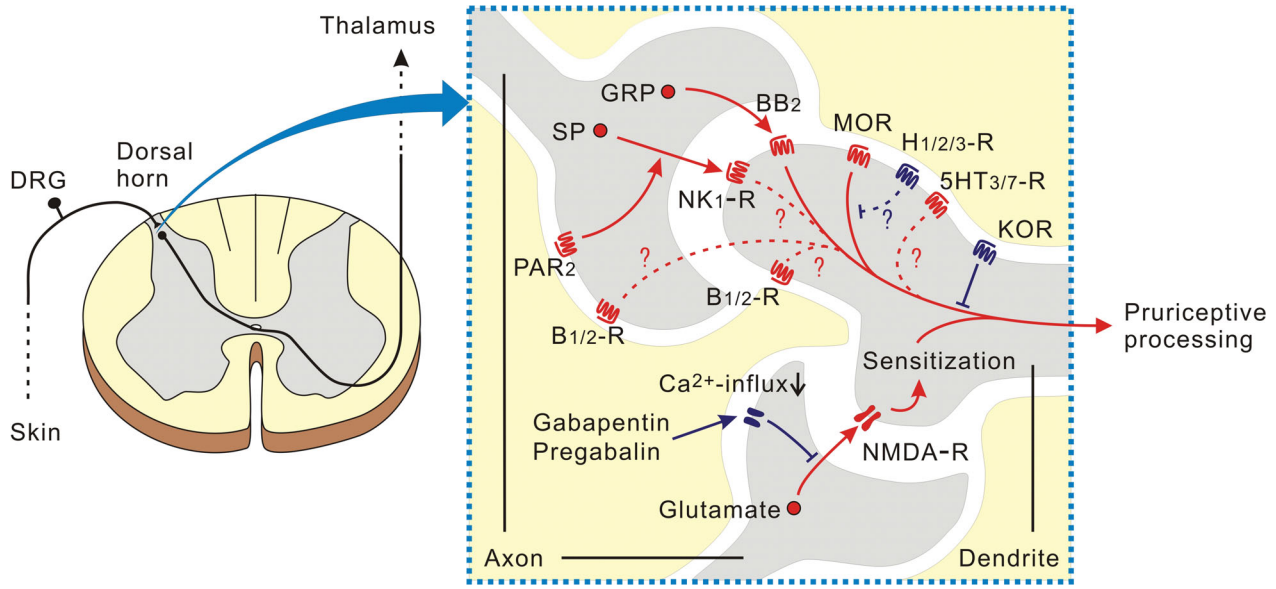
Bradykinin Receptors

Kinins such as bradykinin are formed from their precursors, kininogens, by the action of kallikrein enzymes at the site of trauma and inflammation, and exert their biological effects by acting on a family of G protein-coupled receptors consisting of two subtypes: B_1 and B_2. B_1 receptors are generally absent under physiological conditions, but rapidly upregulated at the terminals of primary afferent sensory neurons under traumatic or inflammatory conditions, whereas B_2 receptors are constitutively expressed in peripheral and central neural tissues [85]. Bradykinin is an important inflammatory mediator that contributes at the skin level to hyperalgesia and allodynia [86]. On the other hand, bradykinin has been shown to play a role as a neurotransmitter in the central nervous system as well [87–89]. For example, bradykinin is released pre-synaptically in the spinal cord in response to nociceptive stimuli, and induces pain hypersensitivity by potentiating glutamatergic synaptic transmission [89]. Although poorly investigated, the involvement of bradykinin in itch induction has also been reported. For example, intracutanously applied bradykinin induced intensive itch in the lesional skin of patients with atopic dermatitis [90]. Sodium deoxycholic acid-induced scratching behavior in rodents seems to be mediated by bradykinin, since B_2 receptor antagonists were effective in blocking pruritus in this setting [91].

The involvement of bradykinin receptors in PAR_2 -mediated itch indicates their roles in pruritus at the central level as well. PAR_2 is activated by various proteases such as trypsin, tryptase, cathepsins, kallikreins, and house dust mite allergens, which are all known to be pruritogens or pruritogen candidates [92,93]. Furthermore, a peptide sequence that activates PAR_2, SLIGRL-NH2, has been used to induce scratching behavior in mice [94]. Neurons responsive to PAR_2 agonists have been identified in the dorsal horn of the spinal cord in rats and mice [76,95]. In a mouse study using Fos-like immunoreactivity (FLI), intradermal injection of histamine induced FLI in the isolectin B_4 (IB_4)-labeled non-peptidergic lamina II of the dorsal horn, whereas SLIGRL-NH_2 caused FLI in the region located dorsal to the IB_4-labeled lamina II. These results suggest distinct pathways for histamine-induced and PAR_2-mediated itch, although another study using an electrophysiological approach has indicated a functional overlap of both pathways [96]. Bradykinin receptors have been indicated to play a role in PAR_2-mediated itch at the spinal cord level [97]. For example, B_1- or B_2-deficient mice are less prone to PAR_2 agonist- and trypsin-induced scratching. Moreover, intrathecal administration of bradykinin receptor antagonists, DALBK (B_1 receptor) and Hoe140 (B_2 receptor), reduced scratching induced by PAR_2, whereas intracerebroventricular administration of these antagonists was not effective [97]. These results strongly indicate the involvement of bradykinin receptors in PAR_2-mediated itch at the spinal cord level. Thus, selective antagonists for bradykinin receptors might be a novel therapeutic option for antipruritic strategies.

Serotonin Receptors

Serotonin (5-hydroxytryptamine, or 5-HT) is a common neurotransmitter located in the gastrointestinal tract and nervous system, and exerts excitatory and inhibitory effects by activating 5-HT receptors. The involvement of serotonin in modulating pain and pain sensitization has been studied for many years and is well known. However, a considerable number of studies also show a role of serotonin as a pruritogen. Although only weak pruritus is elicited in human skin [98], the intradermal application of



Spinal receptors involved in itch induction (for references, see text)

Receptor	Functional relevance to itch induction
MOR & KOR	Epidural administration of morphine, a MOR agonist, induces segmental pruritus. Nalfurafine, a KOR agonist, is effective for hemodialysis-associated pruritus.
BB_2	BB_2-deficient mice, mice pretreated with BB_2-antagonists, and mice in which BB_2-positive nerves were ablated show less scratching behavior for various pruritogens.
NMDA-R	Postsynaptic NMDA-R is activated by glutamate, which induces central sensitization. Drugs inhibiting glutamate release by decreasing Ca^{2+} influx such as gabapentin and pregabalin are effective for neuropathic pain/itch.
NK_1-R	NK_1R-deficient mice and mice pretreated systemically with NK_1-R antagonists show less scratching behavior for spider venom in mice. Aprepitant, an NK1R antagonist, decreases itch in patients with the Sézary syndrome and various kinds of chronic pruritus. Presynaptic PAR_2 activation leads to SP release from the spinal cord.
$B_{1/2}$-R	B_1- or B_2-deficient mice and mice pretreated intrathecally with B_1- or B_2-antagonists show less scratching behavior after PAR_2-agonist application.
$5HT_3$-R	$5HT_3$-R antagonists inhibit morphine-, renal dialysis- and cholestatis-associated itch. Spinal $5HT_7$-R mediates MOR-mediated antinociception, indicating a possible role of $5HT_7$ in itch as well.
$H_{1/2/3}$-R	Antinociceptive effects of morphine are enhanced in H_1-, H_2-, or H_3-R-deficient mice, indicating possible roles of these receptors in morphine-induced itch as well.

MOR: μ-opioid receptor; KOR: κ-opioid receptor; BB_2: bombesin receptor-2; NMDA-R: *N*-methyl-$_D$-aspartate receptor; SP: substance P; NK_1-R: neurokinin-1 receptor; PAR_2: protease-activated receptor-2; $B_{1/2}$-R: bradykinin receptor-1 and -2; $5HT_3$-R: serotonin receptor-3, $H_{1/2/3}$-R: histamine receptor-1, 2, and 3.

serotonin induces a significant scratching behavior in rodents, which is most probably mediated by 5-HT_2 receptors in the periphery [99,100]. In rats and mice, intradermal injection of serotonin exerts a prolonged activation of the superficial dorsal horn neurons that are also responsive to noxious stimuli [101,102], indicating the transmission of serotonin-induced itch via neural pathways that are not itch-specific but conduct both itch and pain.

Serotonin receptors seem to be involved in pruritus at the central level as well. Although morphine antagonizes 5-HT_3 receptors in a concentration-dependent manner in rats [103], clinical studies have revealed that systemically applied ondansetron, a 5-HT_3 receptor antagonist, reduces opioid-induced itch [104,105]. Of note, antipruritic effects of 5-HT_3 receptor antagonists have also been reported in cholestatic and renal pruritus [106,107]. Moreover, spinal 5-HT_7, one of the most recently identified subtypes of serotonin receptors, has been shown to be involved in antinociceptive effects of morphine and tramadol, another drug acting on MOR [108,109], indicating that spinal 5-HT_7 might also be involved in itch induction, since MOR -mediated antinociception is very frequently accompanied by pruritus. The antipruritic effect of drugs acting on other subtypes of serotonin receptors remains to be studied.

Histamine Receptors

Among peripherally acting pruritogenic compounds, histamine is the most extensively studied one both in humans and in animals. The neurons responsible for histamine-induced itch have been identified in a subgroup of C-nerves and the spinothalamic tract. In contrast to the dominant polymodal nerves, histamine-responsive nerves are mechano-insensitive. This supports the theory of the itch transmission via itch-specific neurons [110,111].

Four histamine receptors (H_1, H_2, H_3, and H_4) have been cloned and characterized so far [112]. Histamine-induced neural activation in human skin seems to be mainly mediated via H_1 receptors, because application of H_1 receptor antagonists (H_1 blockers) well suppresses itch and axon-reflex flare induced by experimentally applied histamine [113]. H_1 blockers are indeed effective to inhibit itch in certain subtypes of pruritic diseases such as urticaria in which histamine is released and causes itch. However, histamine is thought to play only a minor role in most other pruritic diseases, since H_1 blockers have only limited therapeutic effects in those diseases. Another possible explanation for the inefficacy of H_1 blockers has been proposed by recent studies showing the involvement of H_4 receptors in inflammation and pruritus [114–117]. In line with these studies, H_4 antagonists have been shown to inhibit scratching behavior induced by histamine or substance P [117–119]. Moreover, H_4 receptors seem to be linked to the pathology of allergic skin inflammation, since H_4 receptor antagonists improve both allergic skin inflammation and pruritus in mice [114]. It is intriguing that intradermal injection of H_3 receptor antagonists increases scratching behavior in mice, indicating that H3R agonists may reduce itch [120]. Substance P in the skin seems to play a role in H_3 antagonism-induced itch [121].

Numerous studies have confirmed a role of histamine and histamine receptors in peripheral itch. However, the impact of histamine receptors on itch at the spinal cord level is poorly understood, although the expression of H_1 receptors in the spinal cord has been demonstrated for a few decades [122–124]. Intrathecal injection of histamine causes pain responses in mice, which seems to be mediated by H_1 receptors, NK_1 receptors, or a polyamine site of NMDA receptors according to recent studies [125–127]. Intriguingly, the involvement of H_1, H_2, and H_3 receptors in morphine-induced antinociception has also been recently indicated in studies using histamine-receptor gene-knockout mice [128–130]. According to these studies, histamine seems to antagonize morphine-induced antinociception via H_1, H_2, and H_3 receptors in the spinal cord. This indicates a possible role of histamine receptors in control of itch as well as pain at the spinal cord level, since morphine apparently induces both pruritus and antinociception via the same spinal MOR [18]. The expression of H_4 receptors in the presynaptic terminals in the laminae I to IV of the spinal cord has recently been demonstrated [131], although their functional role has not been clarified yet. Thus, the involvement of histamine receptors in itch control at various levels including skin, spinal cord, and brain cannot be denied, and drugs that act on histamine-receptors at the spinal cord level might be beneficial to treat certain subtypes of pruritus. Fucusing not only on the localization of histamine receptors but also on how they signal different responses depending on the site of histamine application might be able to highlight important insights into the difference between itch and pain.

Conclusions and Future Perspectives

Identification of receptors specifically related to itch such as KOR and bombesin receptor-2 sheds new light on the complex mechanisms of peripheral and central itch as well as itch sensitization. These receptors are obviously potential targets for the therapy of pruritus. On the other hand, many candidates for itch receptors in the spinal cord such as glutamate receptors and bradykinin receptors are also involved in the pain pathway, as described above, indicating that drugs developed to inhibit pain may also be effective in suppressing itch. This assumption might sound to be contradictory to the general belief that pain inhibits itch and that relief of pain is capable of inducing itch as shown by simultaneous pruritic and antinociceptive effects of MOR agonists. However, it is also true that gabapentin, for example, effectively inhibits some types of itch, such as brachioradial pruritus, as well as postherpetic neuralgia. Thus, targeting spinal neurotransmitter receptors looks promising for the development of novel antipruritic drugs. However, investigations aiming at state-dependent functions of spinal receptors also seem necessary, as a recent primate study has demonstrated that scratching-induced inhibition of spino-thalamic tract neuron activities is dependent on the state of co-existing neural activities.

Among patients suffering from pruritus, we are facing an astounding variation. It also appears that pruritus is regulated by several neuronal as well as non-neuronal cells, and can be modulated (and also pharmacologically manipulated) in different areas such as the skin, DRG neuron, spinal cord, and, finally, selective areas in the brain. In contrast to pain, however, our knowledge about the complex network of itch-related mediators/receptors is still in its infancy. Thus, understanding the different molecular facets of itch induction as well as the mechanisms of central sensitization (and desensitization) during itch transmission and maintenance at the spinal cord level will shed "light" on novel strategies and therapeutic algorithms for those subtypes of pruritus which we currently treat in a "blind" way.

Conflict of Interest

The authors have no conflict of interest.

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